# NTP Research Concept: Triclosan

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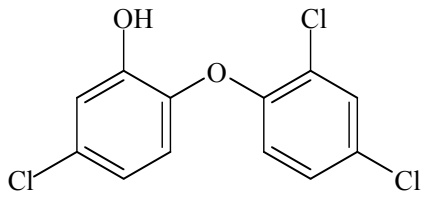
**Background**




Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) was nominated by the U.S. Food & Drug Administration (FDA) and a private individual to the National Toxicology Program (NTP) for dermal toxicity and carcinogenesis studies due to its widespread commercial and personal use as an oral and topical antimicrobial agent (http://ntp.niehs.nih.gov/go/33220).

Triclosan is bacteriostatic at low concentrations (*e.g.* 0.1%) and becomes bactericidal at higher concentrations. The bacteriostatic mechanism of action of triclosan is inhibition of bacterial Type II fatty acid synthase enoyl-reductase. Triclosan has also been reported to intercalate into the bacterial cell walls disrupting membrane activity.

Triclosan has been approved by the FDA for inclusion in toothpastes. It is also in a wide variety of consumer personal hygiene products including hand, facial, and body antibacterial soaps and washes, mouthwash, cosmetics, deodorants, shaving cream, feminine hygiene products, anti-acne products, skin cream and first aid products. The concentration of triclosan in each of the products is dependent on the product, ranging from 0.15-0.3% in spray deodorants, dentrifices, and toothpaste. In addition to the direct application to skin and oral mucosa, triclosan has been incorporated into household items such as kitchen utensils, cutting boards, kitchen wipes, mop heads, computer equipment, clothing, blankets, flooring, paint, air filters, children's toys, and some small appliances. Some medical devices (sutures) have also been impregnated with triclosan to inhibit bacterial growth in wounds. Workplace exposure to triclosan occurs during the manufacture of triclosan-containing products or during use of triclosan-containing products in industrial applications (e.g. use as bacteriocide in buildings).

The absorption, distribution, metabolism and elimination of triclosan have been well studied. Triclosan is glucuronidated or sulfated at the 2'-hydroxy group. Oral administration of triclosan to rats led to plasma half-lifes of triclosan and metabolites of approximately 7-14 hours. The administration of triclosan to the skin of rats resulted in absorption of 6-15% of dose, whereas studies in humans indicated 2-9% of dose absorbed through skin.

The high use of triclosan is reflected by its occurrence in environmental wastewater and presence in human fluids. Triclosan is one of the top seven organic contaminants found in wastewater and stream water in the US and worldwide with concentrations occurring up to 16 µg/L. Triclosan has been detected in human breast milk samples with some samples having no detectable triclosan to some ranging in concentration from 100-

2,100 ng/g lipid (or 36 ng/g whole breast milk). Triclosan has also been detected in human blood plasma and urine, which is probably reflective of widespread use.

Skin toxicity studies have been conducted with triclosan. Dermal application of up to 5% triclosan or 15% triclosan in powdered soap to rats did not result in irritation; however, dermal application has been inconsistent in rabbits with one study reporting some irritation using a 3% solution while other studies using lower concentrations that are commercially relevant were not irritating. A 13-week dermal subchronic toxicity study of triclosan in rats showed dose-dependent signs of severe dermal irritation. These signs were erythema, edema, desquamation, and eschar formation. Microscopically, hyperplasia of sebaceous glands, inflammation, and focal necrosis were seen on the skin of treated animals. The dermal effects were reversible during the recovery period. Acute dermal toxicity studies in humans have not resulted in significant irritation.

Triclosan is not mutagenic or genotoxic. Triclosan has a low level of toxicity in acute studies following oral or intravenous administration with very high $LD_{50}$ values. A battery of reproductive toxicity studies have been conducted under the Colgate Total NDA. No significant treatment-related maternal or fetal toxicities were noted in mice, rats or rabbits up to the highest doses tested.

Several oral chronic carcinogenicity studies have been conducted in rats and submitted to the FDA. In one study triclosan was carcinogenic at 3,000 ppm and in a different study liver hypertrophy was detected at 1,000 and 3,000 ppm.

The major data gap in evaluating the public risk with the use of triclosan is the long term dermal safety profile following triclosan exposure. To date, no acceptable dermal carcinogenesis studies have been conducted.

**Rationale for Studies**

Triclosan is used as an antimicrobial agent in a large number of consumer products in the U.S. and worldwide. It is used commercially, in personal hygiene applications such as handwashes, body washes, toothpastes, and mouth rinses, and in fabrics and plastics to inhibit microbial growth. Triclosan is rapidly absorbed through oral mucosal tissue and skin explaining the occurrence of triclosan in human blood, urine and breast milk. The toxicity studies conducted to date indicate that triclosan does not cause acute toxicity, and has a large margin of safety in chronic oral toxicity studies.

The key data gap at this time in understanding the risk of triclosan is the absence of a valid dermal carcinogenicity study. Triclosan is absorbed through the skin thereby resulting in exposure of the epidermis, epidermal stem cells, and dermis to triclosan. The FDA is requesting evaluation of the dermal carcinogenic potential of triclosan. In addition, exposure of wastewater containing triclosan to environmental ultraviolet light has resulted in the formation of dichlorodibenzo-*p*-dioxins. It is requested that studies be conducted to determine if dichlorodibenzo-*p*-dioxins can form on the skin following application of triclosan and subsequent exposure to ultraviolet light.

**Proposed Approach**

The dermal studies will be conducted in three phases using C3H mice and hairless SKH-1 mice. The latter are being included since it is the animal model typically used in phototoxicity and photocarcinogenicity assays.

The first phase will be to determine the dermal penetration and steady state levels of triclosan in the skin of treated mice. Although dermal penetration studies have been conducted, no studies have examined the kinetics of triclosan in the epidermis and dermis. In order to interpret any dermal toxicity and carcinogenicity studies, knowledge of the target tissue dosimetry (toxicokinetics) is critical. Examination of the target cell concentration following application of triclosan in representative vehicles will provide critical information necessary to design dermal toxicity, carcinogenicity and possibly photocarcinogenicity studies.

As a second phase, upon completion of the toxicokinetic studies, the kinetics of the photodecomposition of triclosan in the skin of mice will be determined. The analysis will focus on photodecomposition products and formation of dichlorodibenzo-*p*-dioxins.

The dermal toxicity will be evaluated on the shaved skin of C3H mice and on hairless SKH-1 mice. This will help in establishing a threshold for dermal tolerance of the applied dose in a representative vehicle that will be used in subsequent dermal carcinogenicity studies. The dermal toxicity studies will consist of an acute exposure to the tolerable topical doses of triclosan, and a 28-day dose-finding study to set the doses to be sued for the chronic dermal carcinogenesis study. Endpoints in the toxicology studies will consist of histopathological evaluation of the skin, and molecular biological and molecular pathology analyses.

The third phase of the proposal will be a dermal carcinogenicity study using the shaved skin of C3H mice in an appropriate vehicle. Data obtained from the acute dermal toxicity studies will be used to set the treatment groups for the dermal carcinogenicity study. Dermal toxicity and dermal carcinogenesis studies should be conducted to quantify the toxic potential.

The data from the kinetic studies and photodecomposition studies will be used to evaluate the triclosan photocarcinogenic risk potential. Photocarcinogenic studies with triclosan will only be conducted if deemed warranted.

**Significance and Expected Outcome**

The outcome of these studies will be to provide the only comprehensive dermal carcinogenicity studies for triclosan which is used in a large number of topical and oral consumer products. The FDA is requesting these data in order to assess whether topical application of this widespread product poses any dermal carcinogenic risk to humans over a life time exposure period.